

24-2594

IN THE

United States Court of Appeals

FOR THE SECOND CIRCUIT

MICHELLE PHIPPEN, INDIVIDUALLY AND AS GENERAL GUARDIAN OF P.P. AND L.A., MINORS, ALISHA DAY, INDIVIDUALLY AND AS GENERAL GUARDIAN OF A.D., A MINOR, SARAH STOKES, INDIVIDUALLY AND AS GENERAL GUARDIAN OF K.G., A MINOR, JUAN EMANUEL BORDOY, INDIVIDUALLY, MARY ELIN ARCE, INDIVIDUALLY AND AS MOTHER OF JUAN EMANUEL BORDOY, AMANDA TRIGLOFF, INDIVIDUALLY AND AS GENERAL GUARDIAN OF R.S., A MINOR, DEANDRE BARBEE, INDIVIDUALLY, JANTAIL BARBEE, INDIVIDUALLY AND AS MOTHER OF DEANDRE BARBEE, LAURIE COURINGTON, HUNTER COURINGTON, JENNIFER MORROW, ALENA MORROW, CALLISTA BASSETT, ANDREW BASSETT, SONNITA ROBY, INDIVIDUALLY AND AS GENERAL GUARDIAN OF D.P., A MINOR, SHANNON MIKUSKI, BRAYDON MCKENZIE,

(Caption continued on inside cover)

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

BRIEF FOR DEFENDANTS-APPELLEES

Jeffrey S. Bucholtz
Amy R. Upshaw
KING & SPALDING LLP
1700 Pennsylvania Ave NW, Ste. 900
Washington, DC 20006
(202) 737-0500

Jay P. Lefkowitz
KIRKLAND & ELLIS LLP
601 Lexington Avenue
New York, NY 10022
(212) 446-4970

Additional Counsel on Inside Cover

HEATHER GILLIAM, COLBY GILLIAM, TAYLOR BROWN, TARYNE BURKE,
INDIVIDUALLY AND AS MOTHER WITH COURT APPOINTED GUARDIAN OF ASHTON
BURKE, SAMARI SIMS, INDIVIDUALLY, DENISA CULLOM, INDIVIDUALLY AND AS
MOTHER OF SAMARI SIMS, COLLIN STOVER, INDIVIDUALLY, DANA STEWART,
INDIVIDUALLY AND AS MOTHER OF COLLIN STOVER, INDIVIDUALLY, DANA
STEWART, INDIVIDUALLY AND AS MOTHER OF COLLIN STOVER, RIAN CZAR
JOHNSON, SHEENA SCHNEPP, INDIVIDUALLY AND AS MOTHER AND NATURAL
GUARDIAN OF H.S., A MINOR, ZAYNE COSTELLO, INDIVIDUALLY, CRYSTAL
ALEXANDER, COURTNEY TILLOTSON, MICHELLE BROWN,

Plaintiffs-Appellants,

—against—

WALGREEN CO., JOHNSON & JOHNSON CONSUMER INC., WALMART INC.,

Defendants-Appellees.

Matthew Noller
KING & SPALDING LLP
50 California St, Suite 3300
San Francisco, CA 94111
(415) 318-1200

*Attorneys for Defendant-Appellee
Walmart Inc.*

Kristen L. Richer
BARNES & THORNBURG LLP
2029 Century Park East, Suite 300
Los Angeles, CA 90067-2904
(310) 284-3896

*Attorney for Defendant-Appellee
Walgreen Co.*

Cole T. Carter
KIRKLAND & ELLIS LLP
333 West Wolf Point Plaza
Chicago, IL 60654
(312) 862-1951

*Attorneys for Defendant-Appellee
Johnson & Johnson Consumer Inc.*

CORPORATE DISCLOSURE STATEMENT

Defendant-Appellee Johnson & Johnson Consumer, Inc. (“JJCI”) has been renamed Kenvue Brands LLC as of October 28, 2024. Kenvue Brands LLC is a wholly owned subsidiary of Kenvue Inc., a publicly held corporation, and, upon information and belief, no publicly held corporation owns more than 10% of Kenvue Inc.’s common stock except for T. Rowe Price Associates, Inc., a subsidiary of T. Rowe Price Group, Inc., a publicly traded company.

Defendant-Appellee Walmart. Inc. has no parent corporation. Walmart Inc. is a publicly traded company. No publicly traded company owns 10% or more of its stock.

Defendant-Appellee Walgreen Co. is owned by Walgreens Boots Alliance, Inc., a publicly traded company. No entity owns more than 10% of Walgreens Boots Alliance, Inc.’s stock.

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PRELIMINARY STATEMENT

This appeal concerns the district court's exclusion of Plaintiffs' general-causation expert Dr. Roberta Ness. After the district court excluded five experts who opined that prenatal acetaminophen exposure can cause both autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD), Dr. Ness submitted an opinion, on behalf of a separate group of Plaintiffs, that acetaminophen can cause ADHD alone. By limiting her opinion to ADHD, Dr. Ness was able to avoid employing the prior experts' "transdiagnostic approach," which the district court rightly found to be unsupported and unreliable. But Dr. Ness could not avoid the other, independently fatal defect in those experts' opinions: that, to buck the overwhelming professional consensus that the available evidence does *not* support a causal relationship between prenatal acetaminophen exposure and any neurodevelopmental issues, it was necessary to resort to outcome-driven reasoning and plucking out favorable results while ignoring the rest. Accordingly, when the district court took the "hard look" at Dr. Ness's report that this Court and Rule 702 require, it found that, like the first set of experts, Dr. Ness had relied on "flagrant cherry-picking," reached conclusions "at odds with the data she cites," and "d[id] not seriously engage" with studies indicating that any association between acetaminophen and ADHD is due to genetic confounding. Those flaws in Dr. Ness's

application of her methodology to the relevant evidence rendered her causation opinion unreliable and inadmissible.

Plaintiffs' opening brief hardly attempts to rebut the district court's substantive criticisms of Dr. Ness's analysis. Instead, Plaintiffs argue that it was inappropriate for the district court to even make those criticisms, because a court should not "evaluate[] the underlying science" when assessing the reliability of an expert opinion under Rule 702. Br. 25. But this Court requires *exactly* that sort of evaluation of the evidentiary basis for an expert's opinion: a district court must undertake a "rigorous examination of the facts on which the expert relies, the method by which the expert draws an opinion from those facts, and how the expert applies the facts and method to the case at hand." *Amorgianos v. Nat'l R.R. Passenger Corp.*, 303 F.3d 256, 267 (2d Cir. 2002). The district court's remarks about "the state of the science Dr. Ness confronted," which Plaintiffs repeatedly cite as evidence that the district court exceeded its role, were thus fully within the mandate of Rule 702. A district court *must* examine the scientific evidence underlying an expert's opinion so that it can assess the opinion's reliability. Otherwise, a district court would have no choice but to greenlight opinions "connected to existing data only by the *ipse dixit* of the expert." *Id.* at 266 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)).

Plaintiffs especially fault the district court for discussing Ahlqvist 2024—a massive study finding that children exposed to acetaminophen *in utero* were no more likely to have ADHD than their unexposed siblings—because the study was published after Dr. Ness submitted her report. But Plaintiffs ignore that the district court made clear it would have excluded Dr. Ness’s opinion “even if Ahlqvist 2024 had not been published,” making all of Plaintiffs’ criticism on this point irrelevant. And in any case, it was perfectly appropriate for the district court to take note of a study, which Dr. Ness had discussed at her deposition and the parties discussed in their briefs, that so thoroughly undermined Dr. Ness’s rationale for discounting the possibility of genetic confounding.

Plaintiffs also contend that, even if the district court properly excluded Dr. Ness, the court should have denied summary judgment and permitted Plaintiffs to mount a general-causation case based entirely on certain statements by Defendants’ expert Dr. Stephen Faraone. Dr. Faraone has never said that prenatal acetaminophen exposure can cause ADHD, as the district court correctly noted. But the more fundamental issue, which Plaintiffs’ brief evades, is that the decontextualized statements that Plaintiffs cobble together do not constitute a reliable analysis of the causation issue that would be admissible under Rule 702. When Dr. Faraone undertook the sort of rigorous analysis that Rule 702 requires, he concluded—consistent with the view of every regulatory

agency and professional organization to opine on the matter—that prenatal acetaminophen exposure does *not* cause ADHD.

Finally, there is an independent ground for affirming the judgment for Defendants: Plaintiffs’ claims are preempted because an FDA regulation (the “Pregnancy Warning Regulation” or “Regulation”) prohibits Defendants from adding the warning that Plaintiffs claim state law requires. The Pregnancy Warning Regulation requires over-the-counter drugs to bear a general warning advising pregnant women to consult with their doctors and provides that, if (and only if) FDA has approved a warning regarding a pregnancy-related risk for a specific over-the-counter drug, that specific warning must *replace* the general warning. Yet the district court concluded that manufacturers can add an *unapproved* warning to *supplement* the general warning whenever state law so requires. That is contrary to the text, structure, and history of the Regulation and FDA’s stated policy of requiring “a single national pregnancy-nursing warning” to “ensure that consumers receive clear, unambiguous, and consistent information on the labeling of OTC drugs.” *Pregnant or Nursing Women; Delegations of Authority and Organization; Amendment of Labeling Requirements for Over-the-Counter Human Drugs*, 47 Fed. Reg. 54,750, 54,756 (Dec. 3, 1982).

This Court should affirm.

COUNTER-STATEMENT OF ISSUES PRESENTED

1. Whether the district court abused its discretion and committed manifest error when it excluded as unreliable the opinions of an expert who cherry-picked favorable results and reached conclusions incompatible with the evidence she evaluated.

2. Whether the district court correctly granted summary judgment to Defendants where Plaintiffs' only evidence of causation consisted of stray statements from a defense expert who opined, in the instant litigation, that there is no evidence that the defendant's product can cause the condition at issue.

3. Whether the Pregnancy Warning Regulation preempts any state-law requirement that a manufacturer supplement the federally mandated general pregnancy warning by adding a warning regarding a specific pregnancy-related risk that is *not* approved by FDA.

STATEMENT OF THE CASE

I. Factual Background

A. Acetaminophen and Its Use During Pregnancy

Acetaminophen has been considered a safe and effective treatment for pain and fever for over half a century. FDA advises women that acetaminophen is generally safe to use throughout pregnancy, unlike ibuprofen, aspirin, and other common pain and fever treatments, which may cause “rare but serious kidney

problems” in infants when used after 20 weeks of pregnancy.¹ Approximately 60% of American women use acetaminophen while pregnant. SPA-11.

The acetaminophen products at issue in this litigation, like most over-the-counter (“OTC”) drugs, are covered by a monograph—“a detailed regulation” issued by FDA that specifies, among other things, what information must appear on the labels of products that fall into a particular “therapeutic class of OTC drugs.” *Nat. Res. Def. Council v. FDA*, 710 F.3d 71, 75 (2d Cir. 2013).² Through the monograph system, a drug can “bypass [the] individualized review” of the “New Drug Application” process and be deemed “generally recognized as safe and effective,” and therefore eligible for sale in the United States, as long as the drug complies with the monograph’s requirements. Acetaminophen belongs to a therapeutic class of pain-, fever-, and inflammation-relieving drugs governed by a monograph. *See* Over-the-Counter (OTC) Monograph M013: Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use (Oct. 14, 2022).

¹ *See* FDA, *FDA Recommends Avoiding Use of NSAIDs in Pregnancy at 20 Weeks or Later Because They Can Result in Low Amniotic Fluid* (Oct. 15, 2020), <https://www.fda.gov/media/142967/download>.

² *See* Congressional Research Service, *FDA Regulation of Over-the-Counter (OTC) Drugs: Overview and Issues for Congress* (Dec. 10, 2021), at 1 (“Although prescription drugs are marketed pursuant to FDA approval via a new drug application (NDA) or an abbreviated new drug application (ANDA), most OTC drug products are marketed under a different mechanism, by complying with an OTC monograph.”).

FDA's Pregnancy Warning Regulation requires the labels for all OTC medications "intended for systemic absorption," including acetaminophen, to state, with the first four words in bold, "**If pregnant or breast-feeding**, ask a health professional before use." 21 C.F.R. § 201.63(a). In promulgating that requirement, FDA explained that "a woman would be best advised on whether to use a particular OTC drug by a knowledgeable health professional who is either familiar with her medical history or readily available to her and capable of assessing her situation with respect to a particular drug." *Pregnant or Nursing Women*, 47 Fed. Reg. at 54,751. The Regulation also provides that, if a more specific warning regarding pregnancy- or nursing-related risks "has been established" by FDA "in a new drug application (NDA) or ... an OTC drug final monograph," then "the specific warning shall be used in place of" the general warning, unless FDA requires otherwise. 21 C.F.R. § 201.63(b). Here, the monograph for acetaminophen's therapeutic class includes specific pregnancy and nursing warnings for aspirin, but not for acetaminophen.

B. Attention-Deficit/Hyperactivity Disorder (ADHD)

ADHD is a neurodevelopmental disorder characterized by a "persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development."³ According to the *Diagnostic and Statistical Manual*

³ American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders* (5th ed., Text Revision, 2022), at 68.

of *Mental Disorders* (“DSM”), a clinical diagnosis of ADHD requires documentation of at least six symptoms of inattention or six symptoms of hyperactivity-impulsivity that persist for a minimum of six months.⁴ Population surveys indicate that ADHD occurs in approximately 7.2% of children.⁵

ADHD is strongly influenced by genetics, with heritability estimated at 74%.⁶ Although there is no single gene for ADHD, studies have identified a number of genetic variants that are associated with the disorder.⁷

C. Studies of Prenatal Acetaminophen Exposure and ADHD.

At the time of the district court’s decision, seven original studies had been conducted on the relationship between prenatal acetaminophen exposure and diagnosed cases of ADHD.⁸ Some studies have found small, unadjusted associations between reported prenatal acetaminophen use and ADHD, although there is substantial divergence regarding which trimesters of usage, or combinations thereof, are associated with a diagnosis. The only meta-analysis limited to studies

⁴ *Id.* at 68-69.

⁵ *Id.* at 71.

⁶ *Id.*

⁷ *Id.*

⁸ Two other studies examined the association between ADHD diagnoses and acetaminophen use postpartum (Ji 2018) or shortly before, during, and immediately after delivery (Ji 2020). SPA-198; *see* A-4520, A-1333.

of ADHD diagnoses, Ricci 2023, concluded that the studies displayed “moderate heterogeneity,” SPA-241, and suggested “a small increase in risk of child ADHD associated with in utero acetaminophen exposure.” SPA-204; *see* A-4446. Ricci 2023 cautioned, however, that “[t]he certainty of the evidence on this topic is low” and called for “future high-quality research.” SPA-204. And indeed, when recent studies have attempted to control for familial factors such as genetics, any statistically significant association between prenatal acetaminophen use and ADHD has disappeared.

The earliest study relevant here, Liew 2014, analyzed maternal interviews at 12 and 30 weeks of pregnancy and found small, statistically significant associations between hyperkinetic disorder (the analog for ADHD in the World Health Organization’s equivalent of the DSM) and prenatal acetaminophen use. The association was present for use during the first trimester alone, the first and third trimesters, and all three trimesters, but not for the second trimester, third trimester, first and second, or second and third. SPA-28; *see* A-4502. The authors cautioned that the associations could be affected by “confounding by indication for drug use”—meaning that the underlying ailment, such as fever, might be contributing to the association—confounding by “ADHD-related genetic factors,” or confounding “by co-exposures to other medications.” SPA-195-96; A-4509.

Liew 2019 examined questionnaires sent every two years to a group of

women, who reported whether they had regularly used a variety of medications in the past two years. SPA-196; *see* A-1385. The study found that ADHD was significantly associated with regular acetaminophen use during a child’s birth year, but not use four years before or four years after. *Id.* Among the women who reported they were pregnant when they completed the questionnaire, the association between acetaminophen use and an eventual ADHD diagnosis was not statistically significant. SPA-197.

Baker 2020 studied 345 children and found that the presence of acetaminophen in meconium—which may indicate acetaminophen use in the second or third trimesters—was associated with ADHD diagnoses. SPA-197; *see* A-1198. The study did not, however, establish a relationship between acetaminophen levels in meconium and mothers’ overall acetaminophen use, and it also did not control for confounding by indication or genetics. SPA-252-53

Chen 2019 reviewed medical records for several thousand mother-child pairs in Taiwan and found a significant association between prescriptions for acetaminophen during pregnancy and an eventual ADHD diagnosis. SPA-200; *see* A-1277. The association was significant for use during “any” trimester, but the associations for use during specific trimesters and combinations of trimesters were not. SPA-200 & n.19. Chen 2019 also found no significant association between ADHD risk and cumulative doses of acetaminophen, leading the authors to conclude

there was no “dose-dependent relationship between prenatal acetaminophen use and the offspring’s ADHD risk.” A-1281.

The four studies discussed above made little attempt, if any, to control for the influence of familial factors, such as genetics, on ADHD diagnoses. Three studies that directly investigated the influence of familial factors have produced results indicating that those factors, and not prenatal exposure to acetaminophen, are driving the associations observed in the other studies.

The first such study was Ystrom 2017, which found a modest significant association between ADHD and prenatal acetaminophen use during the first and second trimesters combined, but not in any individual trimester or all three combined. SPA-201, SPA-242; *see* A-1539. The study also found, however, that the *father’s* use of acetaminophen before conception had a significant association with an eventual ADHD diagnosis. Given that finding, the authors concluded that “the causal role of acetaminophen in the etiology of ADHD can be questioned.” SPA-201. Leppert 2019, a DNA study of thousands of mothers in the U.K., lent support to the theory that genetic confounding is driving the association between prenatal acetaminophen use and ADHD when it found that mothers with high genetic risk for having children with ADHD were also more likely to use acetaminophen during late pregnancy. SPA-233; *see* A-1357.

In the wake of these studies, Gustavson 2021 made the first attempt to control

for familial factors by conducting a sibling-control analysis. A sibling-control study compares the rates of ADHD in children exposed to acetaminophen *in utero* with the rates of ADHD in their unexposed siblings. If acetaminophen exposure were driving the association, rather than a confounding factor like genetics that affects siblings equally, one would expect the rates of ADHD in the exposed and unexposed siblings to be markedly different. Gustavson 2021 evaluated more recent data from the same cohort of children studied in Ystrom 2017 and found that, after factoring in the sibling control, the association between prenatal acetaminophen use and ADHD attenuated to almost zero and became insignificant. SPA-202; *see* A-4539.

A second sibling-control study, Ahlqvist 2024, was published the day of Dr. Ness's deposition. SPA-194-95; *see* A-7530. Ahlqvist 2024 studied a massive dataset—all children born in Sweden for nearly fifteen years—and confirmed acetaminophen use through prenatal medical records. SPA-202. The study found a slight association between prenatal acetaminophen use and ADHD after adjusting for confounders, and the association disappeared completely after applying the sibling control. *Id.* After Ahlqvist 2024's release, the National Institutes of Health issued a news release stating that, according to the study, "[a]cetaminophen exposure during pregnancy is not linked to the risk of autism, ADHD, or intellectual disability." SPA-213.

D. Statements of Regulatory Agencies and Medical Organizations

FDA has been reviewing the scientific literature on prenatal acetaminophen exposure since 2014 and has repeatedly concluded there is *not* support for the claim that acetaminophen causes any adverse neurodevelopmental outcomes, much less ADHD specifically.

FDA opened a “Tracked Safety Issue” on prenatal acetaminophen exposure after the publication of Liew 2014 and recommended that “no regulatory action be taken at this time” but that the agency “stay current on the published safety literature.” SPA-205. In 2015, FDA issued a public Drug Safety Communication about prenatal use of several pain medicines, including acetaminophen. FDA considered studies regarding the association between acetaminophen use and ADHD and found the studies “had a number of methodologic limitations that make the findings difficult to interpret.”⁹ FDA concluded that the “weight of evidence is inconclusive regarding a possible connection between acetaminophen use in pregnancy and ADHD in children.” SPA-206. When FDA reviewed the epidemiological literature again in 2017, it adhered to its position that the available studies “had significant limitations that question the causal effect of [acetaminophen] on adverse neurodevelopmental outcomes.” SPA-206-07. A

⁹ Available at perma.cc/4JY6-CN6V.

January 2018 presentation from the FDA’s Medical Policy and Program Review Council shows that, in light of the available evidence, the Council had rejected the option of requiring revisions to acetaminophen’s label. *See* MDL.Dkt.615-1 at 15.

Professional medical organizations concurred in FDA’s judgment. The Society for Maternal–Fetal Medicine reviewed the scientific literature in 2017 and determined “the weight of the evidence is inconclusive regarding the possible causal relationship between acetaminophen use and neurobehavioral disorders.” SPA-208. And the U.K.’s Royal College of Obstetricians and Gynaecologists advised in 2018 that acetaminophen “remains safe for use during pregnancy and breastfeeding.” *Id.*

In 2021, however, a group of scientists, clinicians, and epidemiologists generated public concern about prenatal acetaminophen exposure when they published a self-styled “Consensus Statement” and “call for precautionary action” in an academic journal. A-4689. The statement acknowledged that the studies of acetaminophen use and neurodevelopmental outcomes “were limited by potential confounding,” including “by genetic factors,” A-4694, but nonetheless asserted that “the combined weight of animal and human scientific evidence [wa]s strong enough” to advise women to limit their use of acetaminophen during pregnancy. SPA-209.

The so-called Consensus Statement elicited a “Consensus Counterstatement” from another group of scientists and clinicians. A-1186. The Counterstatement

concluded—as the Consensus Statement had admitted—that the available studies were “limited by serious methodological problems, including failure to account for confounding.” SPA-210. The Counterstatement therefore “urge[d] against recommending” limitation of acetaminophen use during pregnancy “based on inconclusive and insufficient evidence.” *Id.* The authors of the Consensus Statement replied to make clear that they had “avoided any inference of causality in [the] Consensus Statement” and that their recommendations were precautionary. *Id.*; *see* A-1213.

Professional medical organizations also rejected the claims of the Consensus Statement. The American College of Obstetricians and Gynecologists reviewed the scientific literature and found “no clear evidence that proves a direct relationship between the prudent use of acetaminophen during any trimester and fetal developmental issues.” SPA-211. And the Society of Obstetricians and Gynaecologists of Canada stated its position that “the evidence for causality for this claim is weak and has many fundamental flaws.” SPA-212-13. Sixteen professional organizations and 63 researchers and clinicians also signed a statement that “the available evidence supports neither a change in clinical practice (minimal use when necessary), restricting APAP availabilities to pharmacies, nor additional warning labels on packaging.” SPA-210-11.

After the release of the Consensus Statement, FDA conducted another review

of the scientific literature in 2022, which included 24 new studies since the 2017 review. SPA-207. FDA found that “there are still study limitations and inconsistent study findings that prohibit causal interpretations of the association between APAP exposure and functional neurobehavioral outcomes.” *Id.* The 2022 review also observed that “[u]ntreated fevers during pregnancy are associated with poor pregnancy outcomes,” raising concerns about discouraging pregnant women from using the only fever reliever approved for use during pregnancy. MDL.Dkt.427-7 at 33. FDA’s 2023 review again found that “the limitations and inconsistent findings” of the literature are “unable to support a determination of causality.” SPA-207-08.

II. Procedural History

In 2022, several months after the publication of the Consensus Statement, plaintiffs began filing suit in federal court against the makers and retailers of acetaminophen products, alleging that plaintiffs or their children had developed ASD and/or ADHD due to prenatal acetaminophen exposure. On October 5, 2022, the Judicial Panel on Multidistrict Litigation consolidated the cases in an MDL in the Southern District of New York.

A. The District Court Denies Motions to Dismiss Plaintiffs’ Claims on Preemption Grounds.

Before the formation of the MDL, Walmart moved to dismiss two of the cases brought against it on the ground that the Pregnancy Warning Regulation preempted

the plaintiffs' claims. The district court denied the motions, holding that the Regulation "does not address the ability of manufacturers to supplement the general warning with safety warnings specific to their OTC drug," and then denied a motion for reconsideration. MDL.Dkt.145 at 22-23; MDL.Dkt.601. Johnson & Johnson Consumer Inc. ("JJCI") also filed a motion to dismiss on preemption grounds, and other retailer defendants, including Walgreen Co., incorporated JJCI's argument into their own motion. The court denied JJCI's motion as well. MDL.Dkt.589.

The day before it denied JJCI's motion to dismiss, the court issued an invitation to the United States, "including the Food and Drug Administration," to provide its views on whether the plaintiffs' proposed warning, or any other warning regarding the risks of ASD or ADHD, should be added to acetaminophen labels. MDL.Dkt.588 at 3 (citing 28 U.S.C. § 517). In denying the motion to dismiss, the court noted that "[i]f the United States chooses to respond to this invitation and to declare that the Plaintiffs' proposed label change would result in a misbranding of acetaminophen," then it would revisit the preemption issue. MDL.Dkt.589 at 35. The court notified the parties of its intent to solicit the views of the United States in advance and permitted them to propose edits to the invitation. MDL.Dkt.561. Plaintiffs never objected to seeking the government's views. FDA ultimately declined to submit a statement of interest but submitted a copy of its most recent review of the epidemiological literature. MDL.Dkt.1105.

B. The District Court Excludes the First Set of General-Causation Experts.

Plaintiffs initially put forward five experts with opinions relevant to general causation. The district court excluded each of their opinions on December 18, 2023. As explained in Defendants’ response brief in the first set of appeals, the exclusion order rested on two independent grounds. First, the experts had conducted a single causation analysis for both ASD and ADHD, without adequately explaining why this “transdiagnostic approach” was appropriate for two conditions that have distinct diagnostic criteria and mostly do not afflict the same individuals. Second, even if the transdiagnostic approach to ASD and ADHD were appropriate, the experts had resorted to cherry-picking and outcome-driven reasoning to reach their conclusions, which rendered their opinions unreliable and inadmissible.

Only one of the initial experts, Dr. Baccarelli, conducted a full-length Bradford Hill analysis similar to the one that Dr. Ness performed.¹⁰ Even putting aside the transdiagnostic approach, the problems with Dr. Baccarelli’s analysis ran deep. Three of the deficiencies in Dr. Baccarelli’s report are especially relevant here

¹⁰ Dr. Cabrera conducted a “cursory” Bradford Hill analysis that the district court found unreliable both because Dr. Cabrera failed to weight the Bradford Hill criteria and because, like Dr. Baccarelli, Dr. Cabrera relied on “cherry picking isolated findings, ignoring inconsistent findings, and disregarding limitations expressed by a study’s authors as well as generally accepted statistical principles.” SPA-110; SPA-121.

because they went to the core of his opinion and, despite Plaintiffs’ protests to the contrary, Dr. Ness replicated them in her own report. Indeed, the district court noted that Dr. Ness’s report was “strikingly similar” to Dr. Baccarelli’s. SPA-227.

The first concerns Dr. Baccarelli’s evaluation of the consistency criterion of the Bradford Hill framework, one of the three to which Dr. Baccarelli “assigned the most weight.” SPA-70. The district court found that Dr. Baccarelli had “fail[ed] to engage meaningfully with the inconsistencies among the studies, inconsistencies which exist to a remarkable degree.” SPA-71. The court made clear that “[i]ndividual inconsistencies in the literature do not, by themselves, render Dr. Baccarelli’s opinion unreliable” and that “[i]t is not the strength or lack thereof of the data on which a Rule 702 court must focus.” SPA-81. But Dr. Baccarelli’s “wholesale failure to address the highly heterogeneous nature of the studies” meant that his consistency opinion was “connected to existing data only by the *ipse dixit* of the expert.” *Id.* (quoting *Joiner*, 522 U.S. at 146).

Second, the district court found that Dr. Baccarelli’s consideration of the dose-response criterion, another one of the criteria on which Dr. Baccarelli placed “great weight,” was similarly unreliable. SPA-89. Dr. Baccarelli failed to “grapple” with the “key issue” that none of the studies on which he relied “were able to record the actual dosages taken by pregnant women.” SPA-90. Dr. Baccarelli also relied heavily on Baker 2020—the only study that used an objective biomarker of

acetaminophen use, as opposed to self-report or medical records—for his dose-response opinion, but he did not account for Baker 2020’s failure to control for potential confounders. SPA-90-91.

Third, the district court held that Dr. Baccarelli had “fail[ed] to assess with sufficient rigor the relevant evidence of confounding by genetics.” SPA-94. “A stark example of Dr. Baccarelli’s result-driven analysis” was his praise for Brandlistuen 2013, which he believed cut against genetic confounding, and his “dismissive” treatment of Gustavson 2021, which found that applying a sibling control eliminated any significant association between prenatal acetaminophen use and ADHD. SPA-98-99. Dr. Baccarelli touted the results of Brandlistuen 2013 over those of Gustavson 2021 even though the two studies were conducted on the same cohort of children and only the later study involved formal ADHD diagnoses, while Brandlistuen 2013 had to rely on less well-defined behavioral criteria because the children were not yet old enough to be diagnosed. *Id.* Dr. Baccarelli also had no meaningful response to Ystrom 2017’s finding that ADHD diagnoses were also associated with the father’s preconception acetaminophen use; he could only speculate that paternal use was a proxy for maternal use because “fathers and mothers often share medications.” SPA-100.

After it excluded the initial group of general-causation experts, the district court initiated an order-to-show-cause process that resulted in the entry of final

judgment in all cases where short-form complaints were served on or before January 11, 2024. SPA-180. Those plaintiffs are now parties to the first set of appeals before this Court.

C. The District Court Excludes Dr. Ness’s General-Causation Opinion.

On February 1, 2024, a group of plaintiffs in newly filed cases informed the Court that they intended to offer a general-causation expert of their own, Dr. Roberta Ness. SPA-180-81. Over Defendants’ objection, the district court permitted Plaintiffs to proceed with their new expert and scheduled a new round of Rule 702 briefing. On July 10, 2024, the district court excluded Dr. Ness’s opinion in full.

The district court began its analysis with Defendants’ challenge to Dr. Ness’s qualifications, which the court acknowledged “has force.” SPA-228. Dr. Ness is a physician and epidemiologist whose “research has focused on ovarian cancer, pelvic inflammatory disorder, and preeclampsia.” SPA-225. Unlike Plaintiffs’ initial experts, *see* SPA-228-29, Dr. Ness has “limited professional experience with psychiatry, toxicology, and neurology.” SPA-225. The district court found “Dr. Ness’s lack of expertise in the fields most pertinent to this litigation . . . concerning.” SPA-229. Dr. Ness’s “lack of familiarity with ADHD was apparent at her deposition,” where she was “unable to answer even basic questions about ADHD . . . without reading directly from her report.” *Id.* Her “lack of familiarity with the pertinent literature was also evident.” *Id.* As Dr. Ness acknowledged, she had not

looked at the literature or even “heard of a relationship between acetaminophen and ADHD” before she was retained in this litigation. SPA-226. The district court declined to exclude Dr. Ness as unqualified but noted that “the fact that her opinion was developed for litigation requires a court to undertake a particularly careful examination of the opinion to ensure its reliability.” SPA-231.

The district court started its evaluation of Dr. Ness’s opinion with her treatment of genetic confounding. Dr. Ness acknowledged that, at the time of her report, there were three studies—Ystrom 2017, Leppert 2019, and Gustavson 2021—suggesting that genetic confounding might be responsible for any association between prenatal acetaminophen exposure and ADHD, SPA-231, and she admitted that, “[b]ecause of Gustavson,” she “continue[d] to hold the concern that genetic confounding may *partially* inflate the observed risk between maternal APAP use and ADHD risk.” A-7425. But Dr. Ness ultimately concluded that the evidence did not “support the idea that genetics could *eliminate* the association.” *Id.*

The district court held that Dr. Ness’s downplaying of the evidence of genetic confounding was not reliable. The court explained why Dr. Ness’s treatments of Ystrom 2017 and Leppert 2019 were inadequate, *see* SPA-232-34, but found her discussion of Gustavson 2021 to be “most troubling.” SPA-234. Although Dr. Ness acknowledged Gustavson 2021—a sibling-control study of over 10,000 sibling pairs—as “cause for concern,” she claimed the study had “serious limitations, most

notably its small size.” A-7426. Just as Dr. Baccarelli had, Dr. Ness prioritized the results of Brandlistuen 2013 because there were a larger number of discordant sibling pairs—even though Brandlistuen did not have access to ADHD diagnoses for any of the subjects. SPA-235; *see* A-7424-25.

Additionally, Dr. Ness had stated in her report that, if the results of Gustavson 2021 were replicated, “that would be a cause for greater concern about genetic confounding.” SPA-236; A-7424. That is exactly what happened with Ahlqvist 2024, a much larger sibling-control study that involved more than 31,000 sibling pairs discordant on both exposure and outcome, which also found no association between maternal acetaminophen use and ADHD. The court declined to ignore Ahlqvist 2024 just because it was published after Dr. Ness submitted her report, noting that the parties had addressed the study in their briefs and that Dr. Ness had ample time to supplement her report if she had wished. SPA-237-38. In any event, the court also made clear that it “would reach the same decision regarding Dr. Ness’s reliability even if Ahlqvist 2024 had not been published.” SPA-238.

The district court next turned to Dr. Ness’s Bradford Hill analysis, in which Dr. Ness weighted three factors—consistency, temporality, and dose-response—most heavily. SPA-239. The district court found that Dr. Ness’s discussion of each of these factors “display[ed] results-oriented reasoning, rendering her assessments unreliable.” *Id.*

Regarding the consistency of the association between prenatal acetaminophen exposure and ADHD, the district court found Dr. Ness’s characterizations of the literature to be “faulty” and “at odds with the data she cites.” SPA-241. Dr. Ness claimed that two meta-analyses showed “remarkable consistency” and “no significant heterogeneity,” SPA-240, but the two studies actually acknowledged “moderate” and “substantial” heterogeneity, and one described the certainty of the evidence as “low.” SPA-241. And it was not the case that the “great majority” of studies showed associations in the “second and/or third trimester.” A-7383. As recounted above, *see supra* at 9-11, the trimester-specific results diverged substantially across studies. The only way to conclude otherwise, as Dr. Ness did, was to “ignore statistical significance, cherry-pick data, and ignore contrary findings.” SPA-243. Dr. Ness even cited the reference in the FDA’s 2022 review to “a consistent association between APAP or long durations of prenatal APAP exposure and ADHD,” without acknowledging the very next sentence’s observation that “findings for trimester-specific associations are *not* consistent.” *Id.* (emphasis added).

Dr. Ness’s failure to acknowledge the substantial inconsistency in trimester-specific associations also rendered her analysis of temporality—whether the exposure precedes the development of the disease—unreliable. Despite lacking any relevant professional experience in neurology, Dr. Ness opined that “the greatest risk

from exposure to acetaminophen is in the third and possibly from the middle of the second trimester of gestation,” when “the prefrontal cortex is most sensitive to disruption.” SPA-245. But as the district court pointed out, “only one sub-analysis in the studies cited by Dr. Ness showed a statistically significant positive risk ratio for acetaminophen exposure in the third trimester alone.” SPA-246. Dr. Ness could only conclude that there is an association between ADHD and acetaminophen exposure during the critical period of neurodevelopment through “flagrant cherry-picking,” including “disregard[ing] statistically significant results, or results from studies with large sample sizes, and highlight[ing] insignificant results in their stead.” SPA-247.

Finally, as to the dose-response criterion, the district court found that Dr. Ness had exceeded the limitations of the studies on which she relied, none of which had been able to reliably measure dosage. SPA-251. Dr. Ness “justifie[d] her reliance on crude exposure measurements by a comparison to the government studies of contaminated drinking water at Camp Lejeune,” but the district court pointed out that “duration of exposure was a reasonable proxy for dosage there” because residents would have used similar amounts of drinking water on a daily basis. SPA-251-52. Not so for acetaminophen, which is generally used episodically. Dr. Ness, like Dr. Baccarelli, relied heavily on Baker 2020, which at least used an objective biomarker, but the study did not correlate acetaminophen levels in meconium with

mothers' overall acetaminophen use and did not control for important confounding factors. SPA-252-53.

With respect to the other Bradford Hill criteria, Dr. Ness either found that they were not met (specificity and experiment), only “partially met” (strength), or carried “little weight” (analogy, coherence). SPA-254-55. Dr. Ness assigned biological plausibility moderate weight, but her analysis of the factor was unreliable for the same reasons as that of the first set of experts. *See* SPA-113-22.

In sum, the district court concluded that Dr. Ness's Bradford Hill analysis was “result driven” and “not an objective or rigorous application of scientific methodology.” SPA-257. “Independently,” Dr. Ness's “failure to confront carefully and fairly the profoundly important issue of confounding by genetics renders her opinion on causation inadmissible.” *Id.*

D. The District Court Grants Summary Judgment to Defendants

After excluding Dr. Ness's opinion, the district court ordered Plaintiffs to show cause why final judgment should not be entered in Defendants' favor. SPA-263. In response, Plaintiffs argued that they could carry their burden on general causation by relying on “a handful of prior statements” made by Defendants' expert Dr. Stephen Faraone. SPA-264. These included “two brief excerpts” from Dr. Faraone's deposition, some “statements in peer-reviewed scientific literature or other formal documents,” and other “unsworn statements, principally LinkedIn

posts, which the plaintiffs contend can be admitted for purposes of impeachment.” SPA-268.

The district court rejected Plaintiffs’ argument and entered judgment for Defendants. Because expert testimony is necessary to establish general causation in a pharmaceutical product-liability case like this one, *see* SPA-266-67, Dr. Ness’s exclusion left Plaintiffs with no competent evidence of causation. SPA-268. Dr. Faraone’s prior statements were no substitute. “In none of the statements on which plaintiffs rely” did Dr. Faraone actually “state[] that prenatal exposure to acetaminophen causes ADHD in offspring.” SPA-270. And “[e]ven setting aside the fact that plaintiffs have mischaracterized Dr. Faraone’s prior statements,” their argument “also fundamentally misunderstands the process by which scientists assess the issue of general causation.” SPA-274-75. “[A] series of disparate scientific observations” is not the sort of “thoughtful, reliable analysis by a qualified expert” that Rule 702 requires. SPA-275.

SUMMARY OF ARGUMENT

I. The district court did not abuse its discretion in concluding that Dr. Ness failed to reliably apply the Bradford Hill framework to the evidence regarding the relationship between prenatal acetaminophen exposure and ADHD. The court took “a hard look” at Dr. Ness’s opinion, as it was required to do, to ensure that her methodology was “reliable at every step of the way.” *In re Mirena IUS*

Levonorgestrel-Related Prods. Liab. Litig. (No. II), 982 F.3d 113, 123 (2d Cir. 2020) (*Mirena II*). The court found that, like the first set of general-causation experts, Dr. Ness had to resort to “flagrant cherry-picking” and “result-driven” analysis to downplay the substantial evidence of genetic confounding and inconsistency in results, which have led regulatory agencies and professional organizations to conclude that there is *not* evidence that acetaminophen causes ADHD. Plaintiffs almost completely ignore the court’s explanation of the analytical gaps in Dr. Ness’s opinion, and instead assert that the court excluded Dr. Ness simply because it disagreed with her conclusion. Not so. The district court examined the scientific evidence on which Dr. Ness’s opinion was based, as Rule 702 and this Court’s precedent require, and explained in detail why Dr. Ness had failed to reliably apply her methodology to that evidence.

II. The district court correctly granted summary judgment to Defendants, notwithstanding Plaintiffs’ effort to mount a general-causation case based on a smattering of statements regarding the purported association between acetaminophen and ADHD from Defendants’ expert Dr. Faraone. Dr. Faraone never stated that prenatal acetaminophen exposure causes ADHD, and more fundamentally, stray statements from an expert do not pass muster under Rule 702, which requires an opinion reached after a thorough and fair application of a reliable methodology to all of the relevant evidence.

III. This Court also can affirm the district court’s judgment on the alternative ground that federal law preempts Plaintiffs’ claims. Plaintiffs’ state-law claims flout the comprehensive framework established by the federal Pregnancy Warning Regulation in two ways. First, although the Pregnancy Warning Regulation provides for pregnancy-related warnings that FDA has approved, Plaintiffs argue that state law can require pregnancy-related warnings that have never received FDA scrutiny. Second, according to Plaintiffs, those unapproved warnings must appear *in addition to* the general warning required by the Pregnancy Warning Regulation, even though the Regulation provides that a specific warning (if approved by FDA) should *replace* the general warning, not supplement it. Allowing the tort laws of fifty different states to dictate the piecemeal addition of specific, pregnancy-related warnings—unreviewed by FDA—alongside the FDA-mandated general warning would sow chaos, undermining the agency’s stated policy of requiring “a single national pregnancy-nursing warning” to “help ensure that consumers receive clear, unambiguous, and consistent information on the labeling of OTC drugs.” *Pregnant or Nursing Women*, 47 Fed. Reg. at 54,756.

STANDARD OF REVIEW

This Court reviews a district court’s decision to exclude expert testimony “under a highly deferential abuse of discretion standard.” *Mirena II*, 982 F.3d at 122. “A decision to admit or exclude expert scientific testimony is not an abuse of

discretion unless it is manifestly erroneous.” *Id.* (quoting *Amorgianos*, 303 F.3d at 265). This highly deferential standard of review applies “as much to the trial court’s decisions about *how to determine reliability* as to its ultimate conclusion.” *Id.* (quoting *Amorgianos*, 303 F.3d at 265). A district court thus “has broad discretion in determining ‘what method is appropriate for evaluating reliability under the circumstances of each case.’” *Id.* (quoting *Amorgianos*, 303 F.3d at 265).

This Court “review[s] *de novo* a district court’s application of preemption principles.” *N.Y. SMSA Ltd. P’ship v. Town of Clarkston*, 612 F.3d 97, 103 (2d Cir. 2010).

ARGUMENT

I. The District Court Did Not Abuse Its Discretion in Excluding Dr. Ness’s Opinion.

Plaintiffs’ brief, much like their briefs in the first set of appeals, hardly addresses the specific defects the district court found in Dr. Ness’s analysis, and instead lodges a general complaint that the district court exceeded its role under Rule 702. Because Dr. Ness supposedly “addressed the methodological ‘flaws’” in the initial experts’ opinions, Br. 29, Plaintiffs argue, the district court’s exclusion of Dr. Ness can only be explained by its “disagree[ment] with her conclusions.” Br. 31. In Plaintiffs’ view, the district court’s remarks about “the state of the science,” *id.* (quoting SPA-256), and how it “presents a challenge for any expert witness offering the opinion that [prenatal use of acetaminophen] causes ADHD,” *id.* at 31-32

(quoting SPA-214), made clear that the district court was inappropriately focused on Dr. Ness’s conclusions and their policy implications rather than the “principles and methodology” she employed. *Id.* at 32 (quoting *Amorgianos*, 303 F.3d at 266).

Plaintiffs’ attack on the district court’s motivations is inappropriate and unfounded. If the district court were determined, by any means necessary, to squash any suggestion that prenatal acetaminophen use is associated with neurodevelopmental disorders, then it would not have permitted Plaintiffs to retain a new expert—over Defendants’ objection—to try to offer a stronger general-causation opinion. And the district court’s invitation to the FDA is not, as Plaintiffs suggest, a sign of bias against their position. The district court did not know what the FDA would say in response, and Plaintiffs never objected to the court’s invitation.

The more fundamental problem with Plaintiffs’ argument that the district court gave too much scrutiny to the scientific studies on which Dr. Ness relied, however, is that the argument misunderstands how courts exercise their gatekeeping duties under Rule 702. The Rule does not require a court to evaluate an expert’s “methodology” in a vacuum, without reference to the evidence underlying the expert’s opinion or the conclusions the expert reaches. On the contrary, this Court has made clear that a district court must conduct a “rigorous examination of the facts on which the expert relies” and “when an expert opinion is based on . . . studies that

are simply inadequate to support the conclusions reached, *Daubert* and Rule 702 mandate the exclusion of that unreliable opinion testimony.” *Amorgianos*, 303 F.3d at 266-67; *see also id.* (“[A] district court must examine the expert’s conclusions in order to determine whether they could reliably follow from the facts known to the expert and the methodology used.”) (quoting *Heller v. Shaw Indus.*, 167 F.3d 146, 153 (3d Cir. 1999)).

The district court followed this Court’s guidance, examined the studies that Dr. Ness analyzed in her opinion, and concluded they could not support the conclusions she reached. Those conclusions raised “profound consequences for the health and safety of pregnant women,” as the district court rightly observed during the initial *Daubert* hearing, A-5369-71, because “[f]evers and pain during pregnancy have identified negative impacts on mothers” and medications other than acetaminophen “cannot be used to treat these conditions.” A-5370; SPA-179. But the district court’s exhaustive analysis made clear that it excluded Dr. Ness’s opinion because of her unreliable reasoning, not because of her conclusions’ policy implications. Like the experts in the first set of appeals, Dr. Ness was able to opine that prenatal acetaminophen exposure causes ADHD only by “cherry-pick[ing] from the scientific landscape” and relying on isolated, favorable findings while discounting a larger body of contrary evidence. SPA-244 (quoting *Daniels-Feasel v. Forest Pharms., Inc.*, 2021 WL 4037820, at *4 (S.D.N.Y. Sept. 3, 2021), *aff’d*,

2023 WL 4837521 (2d Cir. July 28, 2023)). That type of “result-driven analysis” infected Dr. Ness’s consideration of genetic confounding and all three of the Bradford Hill criteria on which she relied most heavily, SPA-250 (quoting *Daniels-Feasel*, 2021 WL 4037820, at *5), leaving her opinion with multiple “analytical gap[s] between the studies on which she relied and her conclusions,” which rendered her opinion unreliable. *Amorgianos*, 303 F.3d at 270.

1. Genetic Confounding

The untenable distinction that Plaintiffs draw between methodology on the one hand, and evidence and conclusions on the other, is particularly evident in their discussion of genetic confounding. Plaintiffs contend that Dr. Ness addressed the methodological flaw in the prior experts’ opinions—that, in Plaintiffs’ words, the experts “needed to say more about genetic confounding as part of their Bradford Hill analyses”—by “discuss[ing] this issue in even greater detail.” Br. 30. But the problem was never *how much* the experts said about genetic confounding; the problem was that they cherry-picked favorable evidence and dismissed more probative contrary studies to reach their conclusions.

Dr. Ness relied on the exact same type of cherry-picking as the first set of experts when she discounted the possibility of genetic confounding. One “stark example” of Dr. Baccarelli’s “result-driven analysis” was his decision to downplay the sibling-control result from Gustavson 2021, which suggested that familial factors

rather than acetaminophen exposure are driving the association, in favor of an earlier study of the same cohort of children, Brandlistuen 2013, that did not have access to ADHD diagnoses. SPA-98. Dr. Ness made precisely the same analytical move, privileging Brandlistuen 2013 over Gustavson 2021, *see* A-7424-25, even though she otherwise “relied on studies employing diagnostic endpoints when evaluating the Bradford Hill criteria.” A-7426; *see* Br. 14. Plaintiffs provide no defense of that instance of result-driven analysis, even though the district court found it the “most troubling” aspect of Dr. Ness’s genetic-confounding opinion. SPA-234-35.¹¹

Plaintiffs make much of the district court’s consideration of the sibling-control results from Ahlqvist 2024. But Plaintiffs’ objection betrays their narrow view of Rule 702, under which a court evaluates the expert’s methodology in a vacuum, without any analysis of the evidence from which the expert purports to derive his or her conclusions. Dr. Ness acknowledged in her report that “[b]ecause of Gustavson,” she had a “concern that genetic confounding may *partially* inflate the observed risk between maternal APAP use and ADHD risk,” A-7425, and that

¹¹ Plaintiffs also cite three studies in which the authors expressed doubt that genetics could explain the association between prenatal acetaminophen exposure and ADHD. *See* Br. 21 (citing Liew 2018 and Stergiakouli 2016); Br. 33 (citing Bauer 2018). But the statements in those studies are of little relevance because they predate Leppert 2019 and Gustavson 2021, not to mention Ahlqvist 2024. Plaintiffs cite one more recent article, Br. 33 (citing Jones 2024), but it concerns only ASD and says nothing about ADHD, which is the sole subject of Dr. Ness’s opinion.

“[i]f [Gustavson 2021’s] results were replicated, that would be a cause for greater concern about genetic confounding.” A-7424. The district court was not obligated to blind itself to the reality that Ahlqvist 2024 *did* replicate Gustavson 2021’s results. If Dr. Ness had a sound explanation of why Ahlqvist 2024 did not undermine her opinion, she could have provided that explanation at her deposition or in a supplemental report. But she did not. Without such an explanation, the district court was left with Dr. Ness’s admission that a study exactly like Ahlqvist 2024 would give her even greater concern about genetic confounding, which she had already admitted may be contributing to the association between acetaminophen and ADHD.

The district court was not the first to exclude an expert’s opinion in part because the expert failed to adequately address a study that “was published after [their] report was prepared” and undermined earlier studies on which the expert relied. *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 2015 WL 7776911, at *7 (E.D. Pa. Dec. 2, 2015), *aff’d* 858 F.3d 787, 790 & n.10 (3d Cir. 2017); *see id.* (“Scientists are expected to address and reconcile data that does not support their opinions, and not simply rely upon data which does.”). The district court cited that authority in its decision, SPA-238, and Plaintiffs have never cited any authority to the contrary. An expert should not be permitted to provide the jury with an opinion that subsequent science has fatally undermined, without any opportunity for judicial gatekeeping, simply because the expert submitted his report

before the study was published.

In any case, Plaintiffs’ focus on the district court’s consideration of Ahlqvist 2024 is unwarranted given that the court made clear it “would reach the same decision regarding Dr. Ness’s reliability even if Ahlqvist 2024 had not been published.” SPA-238. Dr. Ness’s methodology is still plagued by cherry picking and results-oriented reasoning, regardless of whether one takes Ahlqvist 2024 into account.

2. Consistency

The district court spent five pages detailing the many analytical flaws—such as “ignor[ing] statistical significance,” “cherry-pick[ing] data,” “ignor[ing] contrary findings,” and “misrepresent[ing] statements by the authors of the studies upon which she relies”—in Dr. Ness’s consideration of consistency. SPA-243-44. Plaintiffs address none of those critiques in the single paragraph they devote to the consistency criterion. *See* Br. 37-38. Instead, they accuse the district court of creating a “rule[]” that “any ‘heterogeneity’ in results means that the consistency criterion cannot be satisfied.” Br. 37.¹² That alleged rule appears nowhere in the

¹² Plaintiffs also suggest that the district court erred in equating “inconsistency” and “heterogeneity,” Br. 37, but they do not explain how these two plain-language synonyms are distinct, and courts often use them interchangeably. *See, e.g., Mirena II*, 341 F. Supp. 3d 213, 264 (S.D.N.Y. 2018); *In re Roundup Prods. Liab. Litig.*, 390 F. Supp. 3d 1102, 1132 (N.D. Cal. 2018); *Zolof*, 2015 WL 7776911, at *11–12.

district court’s opinion. On the contrary, the district court made clear at the outset that “[a]lthough inconsistent results do *not* necessarily rule out a causal nexus, any inconsistencies signal a need to explore whether different results can be reconciled with causality.” SPA-240 (quoting Reference Manual on Scientific Evidence (3d ed. 2011) at 604 (emphasis added)).

The problem was not that the studies were less than perfectly consistent; the problem was that Dr. Ness substantially exaggerated their consistency, particularly at the trimester level. As the district court explained, Dr. Ness ignored that the only meta-analysis of studies involving ADHD diagnoses said that the results displayed “moderate heterogeneity,” SPA-241, and suggested only “a small increase in risk,” SPA-204, and cautioned that “[t]he certainty of the evidence on this topic is low.” *Id.* And Dr. Ness relied on the FDA’s 2022 review without acknowledging its direct statement that “findings for trimester-specific associations are *not* consistent.” SPA-243 (emphasis added). Plaintiffs’ brief offers no defense of Dr. Ness’s treatment of this evidence, and thus gives no grounds to conclude that the district court abused its discretion in finding her consistency opinion unreliable.¹³

¹³ Plaintiffs assert that Dr. Faraone has stated that a 30% association has been consistently observed in the literature, but the testimony Plaintiffs cite says nothing of the sort. Plaintiffs’ attorney asked Dr. Faraone whether one “evidence-based finding[] that is unlikely to be overturned [is] that acetaminophen during pregnancy is associated with a 33 percent greater likelihood of ADHD in children,” and Dr. Faraone responded, “That’s a Taiwanese study, correct,” referring to one specific study. A-4315 (Tr. 363:19–364:2); *see* SPA-273 (discussing this testimony).

3. Temporality

Remarkably, Plaintiffs' brief omits any substantive response to the district court's determination that Dr. Ness did not reliably consider Bradford Hill's temporality criterion, which was one of the three on which Dr. Ness placed the greatest weight. The most Plaintiffs do is assert that Dr. Ness addressed the methodological problem the court identified in the first *Daubert* opinion, where the experts failed to even consider whether acetaminophen exposure preceded the development of ADHD, by opining that acetaminophen "appears to have its greatest impact on neurodevelopment in the third and possibly second trimester," Br. 30 (citing A-7419), which "concorde with current knowledge of when ADHD develops in the fetal brain." A-7433.

But Plaintiffs completely ignore the reason the district court gave for excluding Dr. Ness's temporality opinion: that Dr. Ness "engage[d] in flagrant cherry-picking" to reach her conclusion that acetaminophen appears to have its greatest impact on ADHD risk in the third trimester. SPA-247. As Defendants pointed out, the studies on which Dr. Ness relied "found no statistically significant association between exposure in the third trimester and an ADHD diagnosis, with the majority of studies reporting *lower* effect estimates for the third trimester compared to the first or second trimester." SPA-246 (emphasis added). Dr. Ness could only extract the conclusion Plaintiffs wanted from that body of evidence by

“repeatedly cherry pick[ing] isolated findings in studies, ignor[ing] those that are unsupportive of her ultimate opinion, and highlight[ing] statistically insignificant results while ignoring statistically significant results.” SPA-250. Plaintiffs do not defend Dr. Ness’s application of her methodology from these critiques.

The exclusion of Dr. Ness’s temporality opinion can be affirmed on the additional ground that she is not qualified to offer it. Dr. Ness specializes in women’s health and has “limited professional experience with psychiatry, toxicology, and neurology.” SPA-225. The district court found Dr. Ness’s “lack of expertise in the fields most pertinent to this litigation” to be “concerning,” SPA-229, but “assum[ed]” for purposes of its opinion that Dr. Ness was qualified to opine on temporality. SPA-246. Were this Court to reach the issue, it should hold that Dr. Ness does not possess the requisite qualifications. As the district court observed, Dr. Ness was “frequently unable to answer even basic questions about ADHD” at her deposition, including “when ADHD develops in the fetal brain,” “without reading directly from her report.” SPA-229. Someone who manifestly lacks any independent knowledge of when ADHD develops does not possess the “knowledge, skill, experience, training, or education” necessary to reliably opine about whether the temporality criterion is met in this case. Fed. R. Evid. 702; *see, e.g., Mirena II*, 341 F. Supp. 3d at 251 (excluding physician who lacked expertise in the relevant substantive area); *In re Onglyza (Saxagliptin) & Kombiglyze (Saxagliptin &*

Metformin) *Prods. Liab. Litig.*, 93 F.4th 339, 347 (6th Cir. 2024) (same).

4. Dose-Response

The district court has never held that “only milligram-level data would suffice” to demonstrate a dose-response relationship, as Plaintiffs contend. Br. 39; *see also* 916.Br.41.¹⁴ The problem is that the studies regarding the association between prenatal acetaminophen use and ADHD do not measure dosage *at all*. “Because with rare exceptions acetaminophen is not a prescription medication,” the court explained, “it is difficult to measure the actual amount consumed by pregnant women.” SPA-251. Studies have generally relied on medical records or questionnaires that provide weeks or trimesters of exposure, not the amount of acetaminophen consumed. As the district court observed, one week of exposure “could be one tablet (of unknown dose) or over seven,” and “one trimester could be exposure to one tablet or over 90 or indeed many more.” SPA-252. The district court was right to conclude that an expert cannot provide a reliable dose-response opinion without dosage data.

But the district court also held that, “[e]ven if it were possible to overlook this

¹⁴ Plaintiffs also misleadingly suggest Dr. Faraone has stated there is a dose-response relationship between prenatal acetaminophen use and ADHD, Br. 39, but in fact he was one of dozens of co-authors on an article that merely stated that Ystrom 2017 had “*found* a dose-response relationship.” A-4772 (emphasis added). The article did not mention that Ystrom 2017 had also found that *paternal* use of acetaminophen was associated with ADHD in offspring. *See supra* at 11.

vulnerability in Dr. Ness’s analysis,” her dose-response opinion would still be unreliable because of “her treatment of the studies on which she relies and her failure to discuss other clearly relevant studies.” *Id.* Dr. Ness relied heavily on Baker 2020, but she did not note the authors’ qualification that they “did not correlate maternal acetaminophen use with the acetaminophen concentrations in meconium,” *id.*; she gave too little weight to studies that, unlike Baker 2020, attempted to control for confounding by indication and genetics, SPA-252-43; and she dismissed a contrary study as an “outlier” with “small sample sizes and wide confidence intervals” even though it had “larger sample sizes and narrower confidence intervals” than Baker 2020, SPA-254. Again, Plaintiffs’ brief contains no response to the district court’s detailed demonstration that Dr. Ness evaluated the relevant evidence in an unreliable, result-driven manner.

5. Other Criteria

The district court held that, in addition to Dr. Ness’s failure to reliably address the evidence of genetic confounding, her opinion had to be excluded because her “analyses of the [Bradford Hill] factors upon which she placed the most weight—consistency, temporality, and dose-response—are unreliable.” SPA-256. But “[e]ven if it were possible to rely solely on the additional Bradford Hill factors (and it is not),” Dr. Ness’s opinion would still be subject to exclusion. *Id.*

Dr. Ness assigned only “moderate” weight to the biological-plausibility

criterion, which she stated is “neither necessary nor sufficient for causation.” SPA-255. The district court correctly held that Dr. Ness had failed to reliably describe a biologically plausible mechanism by which prenatal acetaminophen exposure causes ADHD. Plaintiffs repeat the argument, which they also made in the first set of appeals, that the district court is effectively requiring that “the mechanism is known with certainty.” Br. 38; *see* 916.Br.41-42.¹⁵ The district court has not held Plaintiffs’ experts to that standard. Instead, the district court has excluded the experts’ biological plausibility opinions because there are substantial evidentiary “gaps” in the proposed pathways, which the experts filled with their own “*ipse dixit*.” SPA-115. For example, both Dr. Cabrera and Dr. Ness posited that acetaminophen causes ADHD by reducing the levels of the antioxidant GSH, but failed to acknowledge that both studies on the topic show acetaminophen does *not* reduce GSH levels in the brain (as opposed to the liver). SPA-116-117; *see* 916.Resp.Br.47-48.

Moreover, Dr. Ness is not qualified to offer an opinion on the mechanism by

¹⁵ Plaintiffs also quote an attorney’s question to Dr. Faraone to suggest he believes the biological-plausibility criterion is met. Br. 38 (citing A-4307 (Tr. 331:19-332:4)). In the testimony, Dr. Faraone discusses a 2017 LinkedIn post in which he posed the hypothetical question, “[D]oes [an association between acetaminophen and ADHD] make any biological sense?” and then discussed a potential mechanism. *See id.*; A-4306-07 (Tr. 326:25-327:2, 331:6-18). As Dr. Faraone explained in the same answer, the study he was analyzing is, in his view, “no longer interesting because it wasn’t replicated.” A-4307 (Tr. 332:5-6).

which acetaminophen allegedly causes ADHD. The experts who initially opined on biological plausibility, Dr. Baccarelli and Dr. Cabrera, had special expertise in prenatal developmental disorders. *See* SPA-59, -107. But Dr. Ness, as noted above, has no particular expertise in neurology, psychiatry, or toxicology. At her deposition, she could not “provide even a ‘high-level overview’ of her proposed biological mechanism.” SPA-229. Because Dr. Ness’s expertise as an epidemiologist does not qualify her to opine on complex issues outside of her professional training and experience, her biological-plausibility opinion must be excluded. *See Mirena II*, 341 F. Supp. 3d at 251 (excluding biological-plausibility opinion from unqualified physician); *In re Onglyza*, 93 F.4th at 347 (same).

Plaintiffs also assert that it was “error” for the district court to conclude that the strength criterion did not “support a finding of causality.” Br. 38. But not even Dr. Ness believed that the strength of the observed association between prenatal acetaminophen exposure and ADHD was independent evidence of causation. Dr. Ness admitted that the strength of association was only “modest,” found the criterion only “partially met,” and assigned it only “moderate weight” in her Bradford Hill analysis. A-7380-81. Dr. Ness also acknowledged that the relatively weak association made it “more important to examine potential sources of confounding,” A-7381, which supports the district court’s conclusion that Dr. Ness’s unreliable evaluation of genetic confounding independently requires the exclusion of her

opinion.¹⁶

* * *

In reviewing Dr. Ness’s opinion, the district court did exactly what this Court has held Rule 702 requires. The court took a “hard look” at Dr. Ness’s report to ensure her analysis was “reliable at every step of the way.” *Mirena II*, 982 F.3d at 123. And “[i]n deciding whether a step in [Dr. Ness’s] analysis [wa]s unreliable,” the district court followed this Court’s instruction to “undertake a rigorous examination of the facts on which the expert relies . . . and how the expert applies the facts and methods to the case at hand.” *Amorgianos*, 303 F.3d at 267. When the district court reviewed the evidence on which Dr. Ness relied, it found that Dr. Ness (like the experts who preceded her) had only been able to conclude that prenatal acetaminophen exposure causes ADHD through flagrant cherry picking of isolated results and outcome-driven dismissal of contrary findings.

Plaintiffs’ complaint that the district court exceeded its role by evaluating the “state of the science” underlying Dr. Ness’s opinion, therefore, completely misunderstands the Rule 702 inquiry. It is not enough that a qualified expert invokes a recognized methodology, such as the Bradford Hill framework, and provides a written explanation of her reasoning. Instead, a court must review the evidence on

¹⁶ Plaintiffs do not take issue with the district court’s analysis of the other four Bradford Hill criteria.

which the expert relies to ensure that there is not “too great an analytical gap between the data and the opinion proffered.” *Joiner*, 522 U.S. at 146.

Plaintiffs have not provided any substantive rebuttal to the many instances of cherry picking and result-driven reasoning that the district court identified in Dr. Ness’s analysis, and instead rely on a toothless interpretation of Rule 702 that this Court has repeatedly rejected. *See, e.g., Mirena II*, 982 F.3d at 123; *Amorgianos*, 303 F.3d at 267. There is thus no ground to conclude the district court abused its considerable discretion in excluding Dr. Ness’s opinion. As in the appeal from the district court’s first exclusion order, this Court should affirm.

II. The District Court Correctly Granted Summary Judgment to Defendants.

With Dr. Ness’s opinion excluded, Plaintiffs lacked any admissible expert testimony from which a jury could conclude that prenatal acetaminophen exposure can cause ADHD, entitling Defendants to summary judgment on all claims. Plaintiffs protest that the district court should have permitted their case to proceed, with their only causation evidence consisting of prior statements by Defendants’ expert Dr. Stephen Faraone.¹⁷ But Plaintiffs’ last-ditch effort to salvage their claims

¹⁷ Plaintiffs’ brief also references a statement by Defendants’ expert Dr. Alex Kolevzon, Br. 41, but Plaintiffs only identified statements by Dr. Faraone in their responses to the district court’s show-cause order. *See* MDL.Dkt.1497; MDL.Dkt.1509. Plaintiffs thereby forfeited any reliance on Dr. Kolevzon’s statements in opposing summary judgment. In any case, Dr. Kolevzon merely listed acetaminophen as a “potential risk factor” for neurodevelopmental disorders, which

is not even remotely viable. Under Rule 702, expert testimony must be the product of the reliable application of a reliable methodology to the relevant evidence. Stray, isolated statements about the relationship between acetaminophen and ADHD, without any reasoning or consideration of the underlying evidence, obviously do not satisfy the standard, as the district court rightly concluded. And in any event, the district court was also correct that none of the statements, even if admissible, could support a finding of causation.

The most fundamental problem with Plaintiffs' summary-judgment argument is that Plaintiffs cannot string together isolated statements from Defendants' experts to create a reliable causation opinion that satisfies Rule 702. As the district court put it, "none of these statements, either singly or together, constitutes a methodical analysis of the issue of causation," SPA-274, and thus the idea that this collection of "disparate scientific observations is adequate for a jury to find general causation" is "not viable." SPA-275.

Plaintiffs suggest that any Rule 702 objection was forfeited because "[n]o party challenged these opinions of Dr. Faraone . . . under Rule 702, and the District Court cannot raise the issue *sua sponte*." Br. 41. This is simply false. After Plaintiffs responded to the district court's show-cause order by relying on Dr.

could not possibly permit a jury to conclude that acetaminophen causes ADHD specifically.

Faraone’s past statements, Defendants responded by explaining why those bare statements—even when construed as Plaintiffs would like—would not pass muster under Rule 702. *See* MDL.Dkt.1506 at 9 (“[E]ven taken at face value, the brief snippets are certainly not ‘comparable to [admissible] expert testimony in terms of reliability.’”) (quoting *In re Mirena IUD Prods. Liab. Litig.*, 202 F. Supp. 3d 304, 320 (S.D.N.Y. 2016)).

Plaintiffs also assert that they could introduce Dr. Faraone’s past statements as admissions of a party opponent. Br. 41. But Dr. Faraone had no affiliation with any of the Defendants when he made the statements at issue, other than the statements in his deposition testimony. And Plaintiffs’ own authority holds that an expert’s deposition testimony, as opposed to trial testimony, is not admissible as a party admission. *See Glendale Fed. Bank, FSB v. United States*, 39 Fed. Cl. 422, 424 (1997) (“Even at the time of his deposition [the expert] remains autonomous.”).

Plaintiffs offer no serious argument that their compilation of Dr. Faraone’s past statements satisfies Rule 702. They point to the undisputed fact that Dr. Faraone is a qualified expert, Br. 42-43, but that does not mean any statements attributed to him are automatically admissible opinions. Plaintiffs also argue that a Bradford Hill analysis is not the only reliable methodology for assessing causation, but the problem with Dr. Faraone’s isolated, out-of-context statements is that they do not result from the application of *any* methodology, much less the application of a

reliable methodology to all relevant evidence.

In any event, Dr. Faraone's statements would not support a finding of causation even if they were admissible as expert opinion testimony. As the district court explained, "[i]n none of the statements on which plaintiffs rely does Dr. Faraone state that prenatal exposure to acetaminophen causes ADHD in offspring." SPA-270. Many of the statements did not even refer to acetaminophen, SPA-270-71, and others referred only to an *association* between acetaminophen and ADHD. SPA-271-72. On appeal, Plaintiffs especially stress that Dr. Faraone included acetaminophen on a slide listing more than a dozen "environmental risk factors" for ADHD, which came after a title slide that read "Causes of ADHD." Br. 6-7. But, as the district court noted, Dr. Faraone explained that "the term 'risk factor' is a synonym for 'correlate' and that 'it's not the same as cause.'" SPA-272. No reasonable jury could find causation based purely on a slide labeling acetaminophen a "risk factor," when the slide's author has explained he did not intend to assert that acetaminophen causes ADHD and, moreover, reached the exact opposite conclusion after a thorough and methodical analysis. Plaintiffs engage in even more blatant cherry picking than their expert by lifting stray statements out of context and prioritizing them over Dr. Faraone's stated opinions.

III. In the Alternative, Plaintiffs' Claims Are Preempted by Federal Law.

Plaintiffs' claims also fail for the independent reason that their proposed

warning conflicts with FDA’s comprehensive regulatory framework governing warnings about pregnancy-related risks posed by OTC drugs. Because federal law bars Defendants from adding an unvetted warning about the putative risks of ADHD, Plaintiffs’ state-law claims—all of which are predicated on the absence of such a warning—are preempted.¹⁸

Federal regulations preempt state law when promulgated “within the scope of [an agency’s] congressionally delegated authority.” *Merck Sharp & Dohme Corp. v. Albrecht*, 587 U.S. 299, 315 (2019) (quoting *New York v. FERC*, 535 U.S. 1, 18 (2002)). FDA exercised its delegated authority to promulgate the Pregnancy Warning Regulation, mandating a verbatim general warning and creating a process for FDA to provide for different warnings when warranted for specific products. The relevant question, as the district court recognized, is whether Defendants “could have unilaterally strengthened warnings on [their] label[s] without prior approval from the FDA.” MDL.Dkt.145 at 17. If not, then “compliance with both state and federal law is a physical impossibility,” and the state law requiring an additional

¹⁸ Below, Defendants argued for preemption on the additional ground that there is “clear evidence” FDA would reject Plaintiffs’ proposed warning, given that FDA has repeatedly concluded that there is insufficient evidence of causation. *See* MDL.Dkt.589 at 30-37. The district court deemed that argument “premature,” stating that *Daubert* motions may shed light on the issue. *Id.* at 31. Defendants do not raise this distinct preemption argument as an alternative ground for affirmance only because it is too fact-bound for this Court to decide in the first instance.

warning is preempted. *Marentette v. Abbott Labs., Inc.*, 886 F.3d 112, 117 (2d Cir. 2018) (quoting *Arizona v. United States*, 567 U.S. 387, 399 (2012)). Under the Pregnancy Warning Regulation, compliance with both state and federal law is impossible: Defendants are required to give the verbatim warning mandated by the Regulation unless and until FDA, via the process set forth in the Regulation, mandates a different warning.

In response to California’s adoption of regulations requiring drugmakers to warn about pregnancy-related risks, FDA issued the Pregnancy Warning Regulation in 1982. The purpose of the rulemaking was to create “a single national pregnancy-nursing warning with a specified text” so that manufacturers would have to use the FDA-mandated warning rather than any different warning required by a state. *Pregnant or Nursing Women*, 47 Fed. Reg. at 54,756. FDA explained that a uniform national warning would “ensure that consumers receive clear, unambiguous, and consistent information” and thus was “necessary to ensure that OTC drugs are used safely and for their intended purposes.” *Id.* The Regulation’s “text, structure, history, and purpose” all establish that it is exclusive and preemptive. *Kisor v. Wilkie*, 588 U.S. 558, 575 (2019).

The Pregnancy Warning Regulation now provides, in relevant part, that:

(a) The labeling for all over-the-counter (OTC) drug products that are intended for systemic absorption, unless specifically exempted, shall contain a general warning under the heading “Warning” (or “Warnings” if it appears with additional warning statements) as follows: “**If**

pregnant or breast-feeding, ask a health professional before use.”

(b) Where a specific warning relating to use during pregnancy or while nursing has been established for a particular drug product in a new drug application (NDA) or for a product covered by an OTC drug final monograph in part 330 of this chapter, the specific warning shall be used in place of the warning in paragraph (a) of this section, unless otherwise stated in the NDA or in the final OTC drug monograph.

21 C.F.R. § 201.63.

Paragraph (a) sets forth the default rule that all covered OTC drugs must bear the “general warning” advising women who are pregnant or breastfeeding to consult a medical professional before taking the product. *Id.* § 201.63(a). The label must repeat the “exact language” provided by the Regulation. 21 C.F.R. § 330.1(c)(2). Any deviation renders the product misbranded under federal law. *See id.* FDA has explained that this exact-language requirement effectuates the agency’s “exclusivity policy,” which “limit[s] monograph labeling terminology to specific words and phrases considered and approved by FDA.” *Limitations of Labeling Terminology*, 47 Fed. Reg. 29,002, 29,002 (July 2, 1982). Indeed, in the Pregnancy Warning Regulation rulemaking, FDA explained that uniformity was so important that differing state warnings were not permitted even if the differences were only non-substantive variations in wording. *See Pregnant or Nursing Women*, 47 Fed. Reg. at 54,754 (“Alternative language will not be accepted.”).

Paragraph (b) then describes circumstances in which a “specific warning” must be “used in place of” the general pregnancy warning. A specific warning will

replace the general warning if, and only if, “a specific warning relating to use during pregnancy or while nursing has been established for a particular drug product in a new drug application (NDA) or for a product covered by an OTC drug final monograph.” A warning can be “established” in an NDA or monograph only if FDA approves it. When FDA issued the Regulation, it explained that “a specific pregnancy-nursing warning that is required in a final OTC drug monograph [or NDA] *supersedes* the general warning,” unless otherwise stated in the monograph or NDA. *Pregnant or Nursing Women*, 47 Fed. Reg. at 54,755 (emphasis added).

Plaintiffs’ putative state-law duty to add a specific warning about the alleged risk of ADHD is in irresolvable conflict with the federal regulatory scheme governing pregnancy-related warnings for OTC drugs. The Regulation must be read as creating an exclusive process for adding warnings regarding specific pregnancy-related risks. If state law could dictate the inclusion of such warnings, then the conditions the Regulation puts on the addition of those warnings would be superfluous. And state law could require that unapproved warnings *supplement* the FDA-mandated general warning, even though FDA determined that FDA-approved specific pregnancy-related warnings should be used “in place of” the general warning, unless an FDA-approved NDA or monograph provides otherwise. 21 C.F.R. § 201.63(b). This would have the absurd consequence of prohibiting a manufacturer from making even purely stylistic changes to the phrasing of FDA’s

general warning but allowing the same manufacturer to add entirely new specific warnings that significantly change the overall message without any agency oversight at all.

Because the Pregnancy Warning Regulation creates an exclusive process for adding pregnancy-related warnings to an OTC drug's label, it is "a physical impossibility" for Defendants to comply with both the Regulation and Plaintiffs' asserted state-law duty. *Marentette*, 886 F.3d at 117. Defendants cannot add Plaintiffs' preferred warning to acetaminophen's label because the Regulation: (1) only authorizes specific warnings that "ha[ve] been established" by FDA; and (2) requires such warnings to be used "in place of" the general warning, unless FDA provides otherwise. 21 C.F.R. § 201.63(b). Plaintiffs' putative state-law duty thus conflicts with federal law and is preempted.

The history and purpose of the Pregnancy Warning Regulation confirm that it excludes and preempts any differing state-law requirements. In promulgating the Regulation, FDA explained that it establishes "a single national pregnancy-nursing warning with a specified text" and concluded, after notice and comment, that "differing State OTC drug pregnancy-nursing warning requirements" would be "preempted by the regulation as a matter of law." *Pregnant or Nursing Women*, 47 Fed. Reg. at 54,756. Permitting "[d]iffering State requirements" to go into effect, FDA observed, would "conflict with the Federal warning, cause confusion to

consumers, and otherwise weaken the Federal warning,” which would “prevent accomplishment of the full purpose and objectives of the agency in issuing the regulation.” *Id.* Under the Regulation, therefore, manufacturers are “able to use the new FDA labeling *without also being required to use the pregnancy-nursing warning labeling required by any State.*” *Id.* at 54,757. (emphasis added).

FDA’s interpretation of the Regulation as exclusive and preemptive follows from the Regulation’s text and structure. But even were the Court to find the Regulation ambiguous, FDA’s contemporaneous interpretation of its own Regulation, to which it has adhered for over forty years, would be entitled to deference. *See Kisor*, 588 U.S. at 574-75; *Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 883 (2000) (giving weight to agency’s interpretation of its regulations to preempt a state-law tort suit). FDA’s interpretation of its Regulation as exclusive is an “authoritative” construction, adopted through notice-and-comment rulemaking, that reflects the agency’s “fair and considered judgment.” *Kisor*, 588 U.S. at 577-79. And FDA’s choice to exercise its delegated authority to create a verbatim national warning, along with a process to vary the warning where appropriate, reflects a policy judgment about the best way to communicate potential risks to pregnant and nursing patients that implicates the agency’s “substantive expertise” in public health. *Id.* at 577-78.

The district court nonetheless concluded that Plaintiffs’ claims were not

preempted because the Regulation “does not address the ability of manufacturers to supplement the general warning with safety warnings specific to their OTC drug.” MDL.Dkt.145 at 22-23. But, as explained above, paragraph (b) must be read as creating the exclusive process for adding specific pregnancy-related warnings to OTC labels. Otherwise, state law could require any number of specific warnings to appear alongside the general warning, in contradiction of FDA’s determinations that specific warnings must be approved by FDA and, unless FDA says otherwise, must replace the general warning, not “supplement” it. *Id.*

The court thought it implausible that the Pregnancy Warning Regulation would “bar[]” manufacturers “from adding to their labels truthful warnings about use of their own drugs during pregnancy” because such a rule “would constitute a massive shift from a foundational principle ... that manufacturers are responsible at all times for the adequacy of their drug labels.” MDL.Dkt.589 at 23. The district court drew that principle from *Wyeth v. Levine*, 555 U.S. 555 (2009), but *Wyeth* did not involve a situation like this one, where FDA promulgated a specific regulation to govern a particular class of warnings. Indeed, in his concurrence, Justice Breyer distinguished between *Wyeth* and cases like this by emphasizing the Court’s statement that “we have no occasion in this case to consider the pre-emptive effect of a specific agency regulation bearing the force of law.” 555 U.S. at 581. Justice Breyer noted that FDA is empowered to “determine whether and when state tort law

acts as a help or a hindrance to achieving [] safe drug-related medical care” and “may seek to embody those determinations in lawful specific regulations describing, for example, when labeling requirements serve as a ceiling as well as a floor.” *Id.* at 582.

The Pregnancy Warning Regulation is precisely the sort of “lawful specific regulation[]” that establishes “a ceiling as well as a floor” and thus has “pre-emptive effect.” *Id.* The general warning must be included unless FDA has approved a specific warning for the product, in which case, unless FDA directs otherwise, the specific warning takes the general warning’s place. State-law duties to add *unapproved* warnings to *supplement* the general warning—rather than *approved* warnings to *replace* it—are incompatible with federal law and thus preempted.

CONCLUSION

For the foregoing reasons, the Court should affirm.

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Respectfully submitted,

/s/ Jeffrey S. Bucholtz

Jeffrey S. Bucholtz
KING & SPALDING LLP
1700 Pennsylvania Ave NW
Suite 900
Washington, DC 20006
(202) 737-0500

*Attorney for Defendants-Appellees
Walmart Inc. and Sam's West, Inc.*

/s/ Cole Carter

Cole Carter
KIRKLAND & ELLIS LLP
333 W Wolf Point Plaza
Chicago, IL 60610
(312) 862-1951

*Attorney for Defendant-Appellee
Johnson & Johnson Consumer Inc.*

/s/ Kristen L. Richer

Kristen L. Richer
BARNES & THORNBURG LLP
2029 Century Park East, Suite 300
Los Angeles, CA 90067-2904
(310) 284-3896

*Attorney for Defendant-Appellee
Walgreen Co.*

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April 2, 2025

/s/ Cole Carter
Cole Carter

*Attorney For Defendant-Appellee
Johnson & Johnson Consumer
Inc.*

CERTIFICATE OF SERVICE

I hereby certify that, on April 2, 2025, an electronic copy of the foregoing Brief for Defendants-Appellees was filed with the Clerk of Court using the ECF system and thereby served upon all counsel appearing in this case.

/s/ Cole Carter
Cole Carter

*Attorney For Defendant-Appellee
Johnson & Johnson Consumer
Inc.*